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Pandemic Influenza Vaccines and Vaccine Development

Challenges and opportunities

Dr. Prakash Sambhara
Influenza Division
Centers for Disease Control and Prevention
Atlanta GA 30333 USA
ssambhara@cdc.gov

CDC

Influenza Pandemics

3 pandemics of influenza in 20th century

- 1918 Spanish Flu pandemic caused at least 675,000 U.S. deaths and up to 50 million deaths worldwide

- 1957 Asian Flu pandemic caused at least 70,000 U.S. deaths and 1-2 million deaths worldwide

- 1968 Hong Kong Flu pandemic caused about 34,000 U.S. deaths and 700,000 deaths worldwide

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Prevention and Control of influenza

Vaccines

1940s: Egg-based inactivated vaccines

2003: A live, attenuated, cold adapted, temperature sensitive, trivalent influenza virus vaccine (LAIV) was licensed in the United States.

Antiviral drugs for prophylaxis and treatment

1966: M2 Ion-channel blockers: inhibit the replication of influenza A viruses by interfering with the uncoating of the virus inside the cell

1999: Neuraminidase inhibitor (Oseltamivir): prevents the release of new viral particles from infected cells

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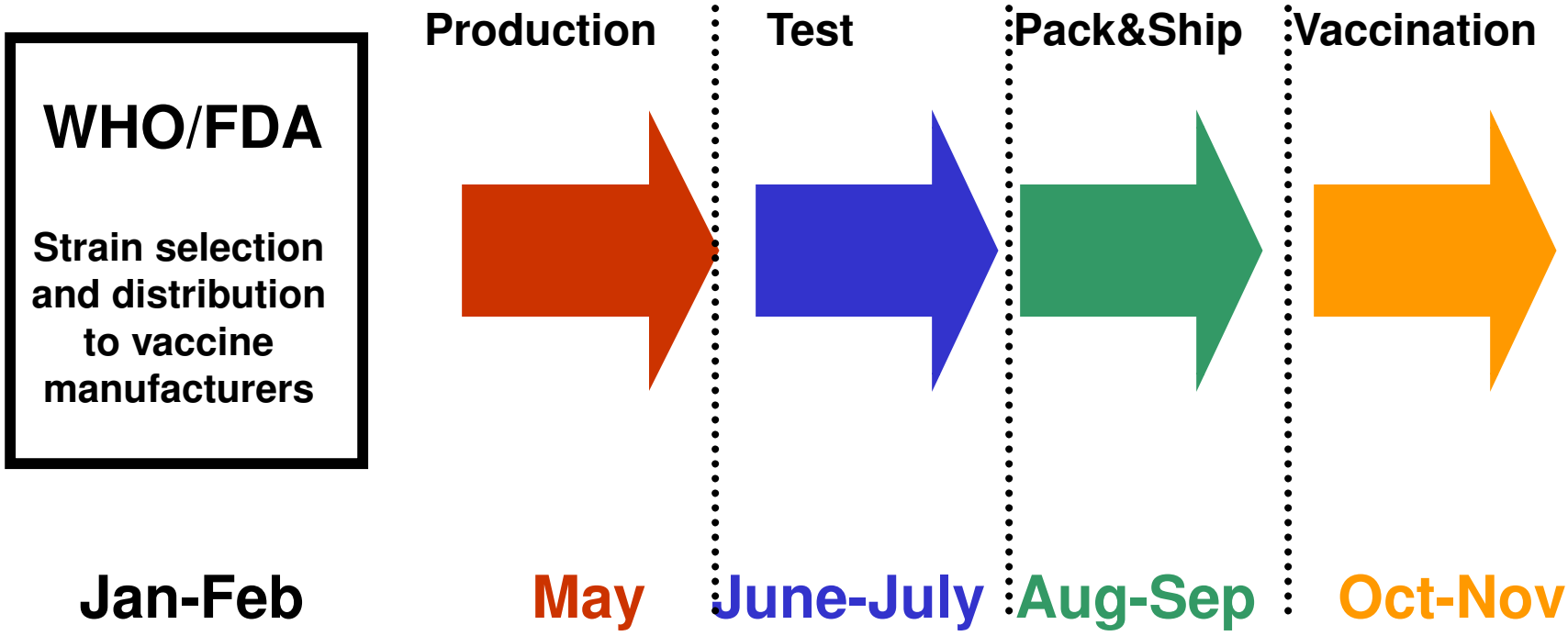
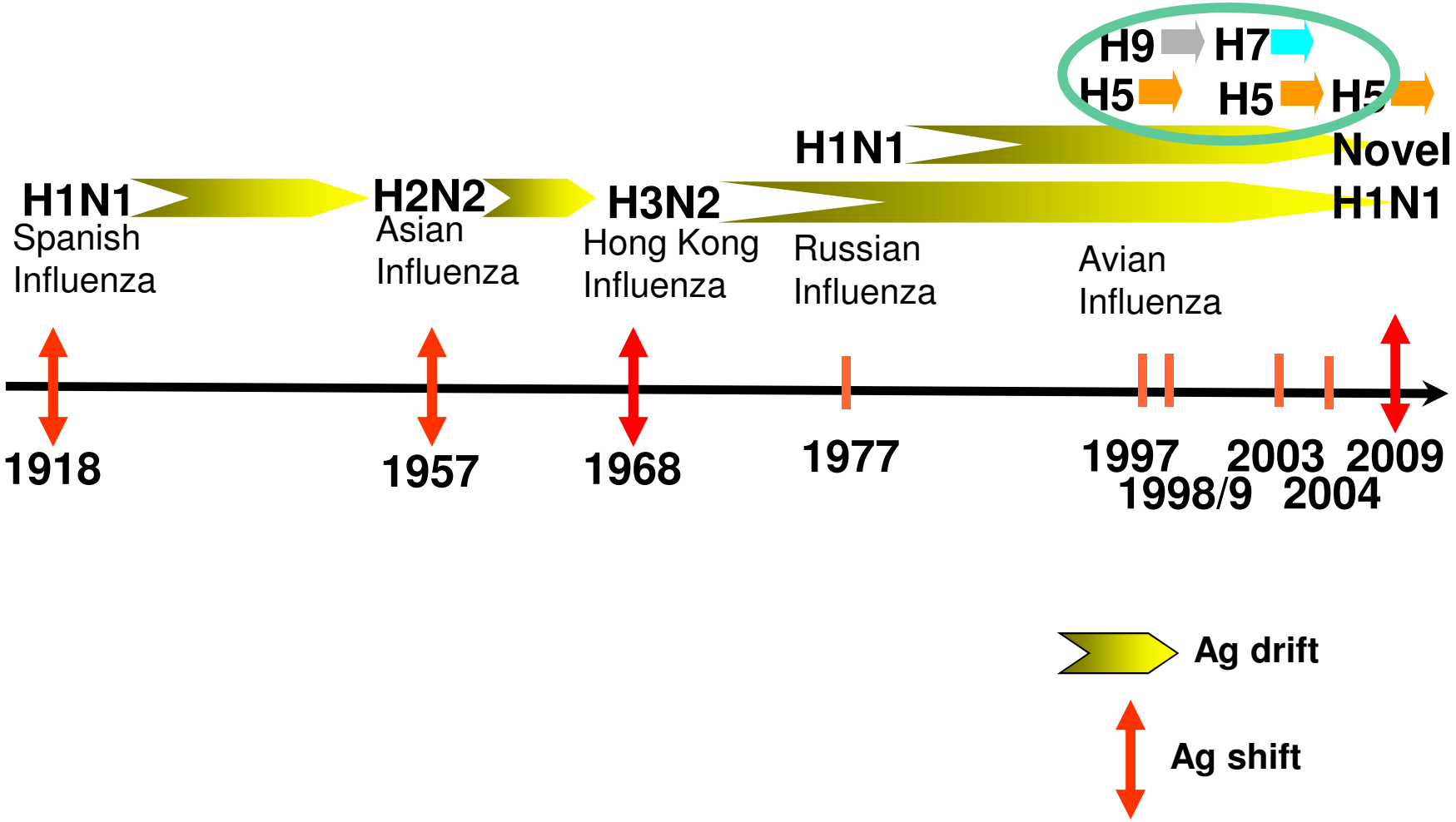
Preventive vaccination is the most cost-effective public health intervention strategy to protect the population

Timeline of influenza vaccine production: Egg-based technology



- Inactivated split virus vaccines: Sanofi, GSK, Novartis, CSL, Solvay and others
- Live attenuated: FluMist, Astra Zeneca; Microgen

Emergence of Influenza A Viruses in Humans



Current situation with Avian Influenza H5N1 viruses

- H5N1 viruses detected in birds in 65 countries
- 12 countries reported 504 confirmed human cases with 299 fatalities (about 60% case fatality) due to H5N1 virus infection since 2003
- Virus has drifted into several different clades
  - Multiple subclades in each clade
- Potential of anti-viral resistance
- Currently licensed tri-valent seasonal vaccines consisting of H1N1, H3N2, and B components do not provide protection against H5N1 viruses

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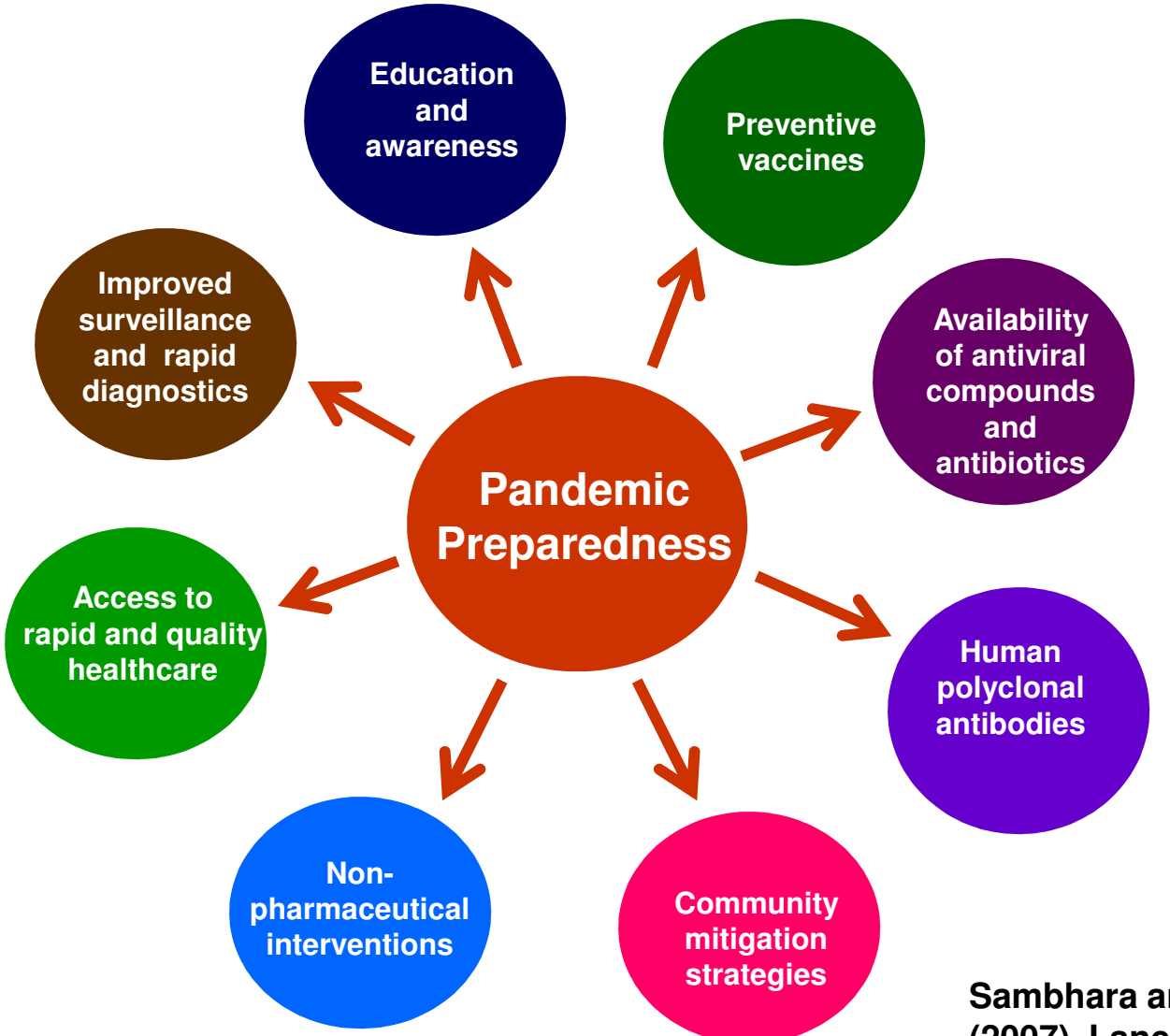
Global Public Health Measures



Sambhara and Poland (2007), Lancet

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Pre- pandemic H5N1 influenza Vaccines

- Egg-derived rgH5N1 vaccines
- Clade 1 vaccine
  - Needed at least 2 doses of split vaccine at 90μg/dose (Treanor et al 2006) **53%** of the vaccinees had a neutralization titer of ≥40
  - 2 doses of split vaccine 30μg with alum as an adjuvant (Bresson et al 2006) **41%** of vaccinees had 4-fold increase in neutralization titers
  - 2 doses of whole-inactivated vaccine at 10μg with alum as an adjuvant (Lin et al 2006) **50%** of the vaccinees had a neutralization titer of ≥40.

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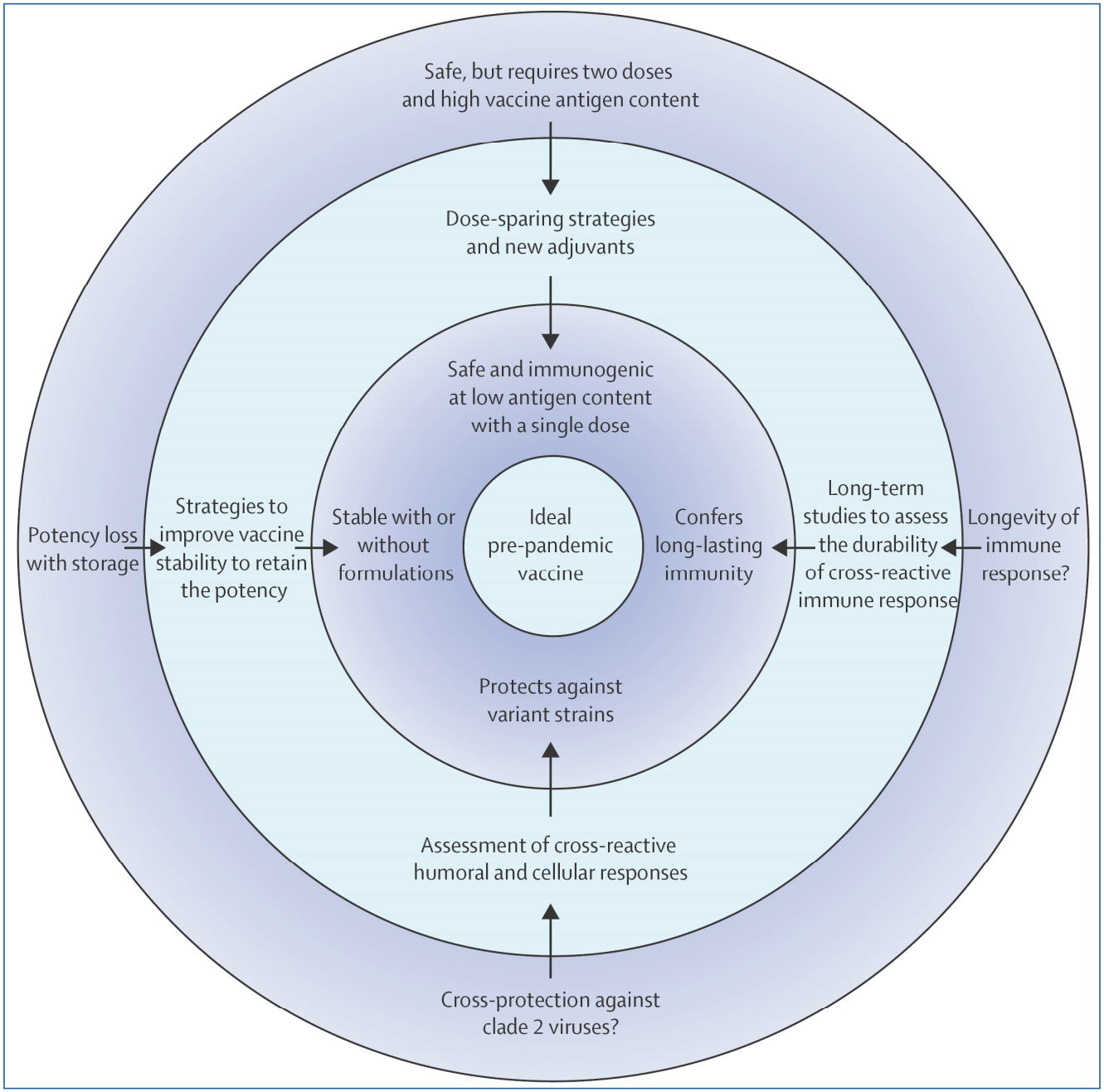

Figure: "Target" paradigm of H5N1 pandemic vaccine development

Sambhara et al (2007), Lancet Infect Dis

Challenges: Vaccine availability in a H5N1 pandemic 2004-05

Influenza vaccines are egg-derived. H5N1 viruses are highly lethal to poultry. Availability of eggs for vaccine production in the event of a H5N1 pandemic?

The global demand for vaccines will be > 4-8 billion doses to prevent/contain a pandemic that results in high case fatality. Existing vaccine production capacity (300 million trivalent doses) cannot meet the demand

- Adjuvants to enhance immunogenicity and achieve antigen dose-sparing
- Exploring egg-independent vaccine production strategies

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Ideal Adjuvant/Formulation

1. Safe (alone or in combination, potential risk vs benefit)
2. Biodegradable
3. Induces robust immune response
4. Chemically and biologically well defined
5. Antigen dose-sparing
6. Stable
7. Affordable and available without any restrictions
8. Induces humoral and cellular immunity

Pre- pandemic influenza Vaccines

Egg-derived rgH5N1 vaccines with oil-in-water emulsions

GSK

- **2 doses of 3.8μg with ASO3**

Sanofi

- **2 doses of 3.75μg of antigen with AFO3**

Novartis

- **2 doses at 7.5μg with MF59**

Resulted in significant seroprotection rates (>80%) and cross-clade reactivity

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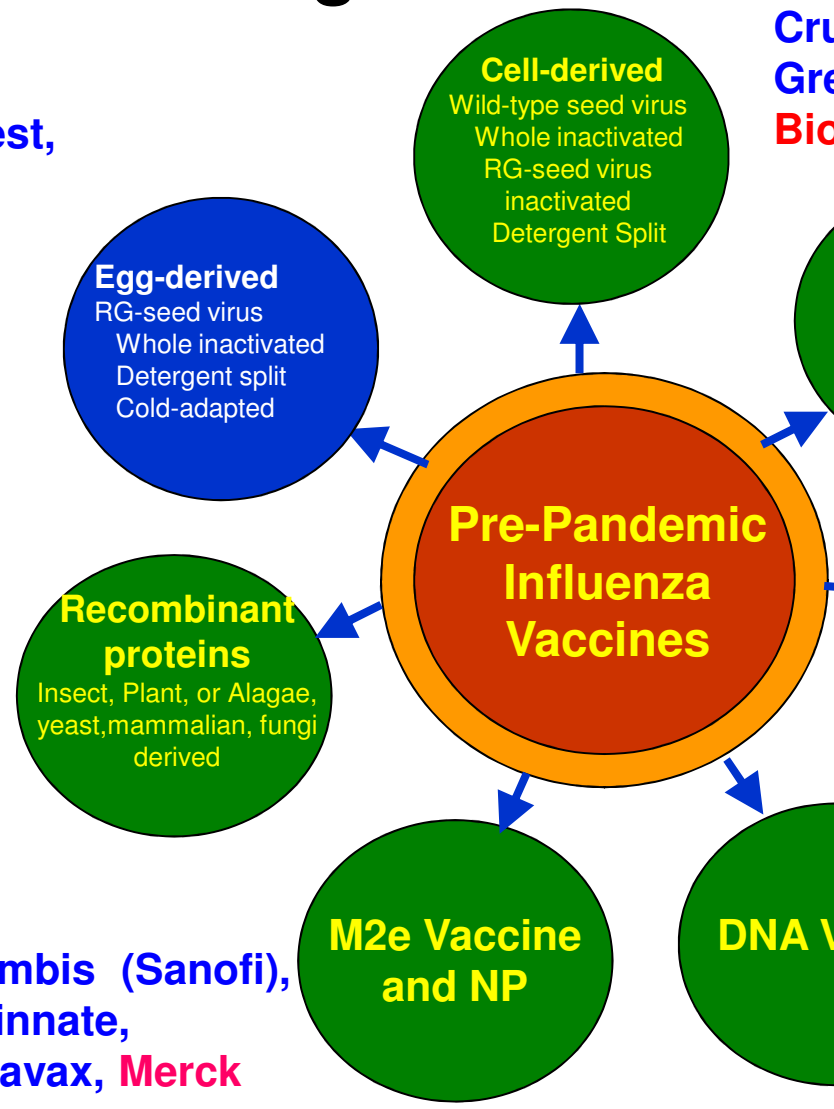
Vaccine Technologies



Baxter,
Novartis, GSK, Solvay,
Crucell,
Green Hills Biotech, Vivaldi
BioSciences, FluGen

Sinovac, Omnivest,
Novartis,GSK,
Sanofi, CSL,
Medimmune,
Microgen

PaxVax, Vaxin,
VRC, GenVec,
AlphaVax, Vaxart

Protein Sciences
Fraunhofer
Globeimmune
Neurogenesis

Novavax
Ligocyte
Medicago
Technovax
Epixis

Acambis (Sanofi),
Vaxinnate,
Dynavax, Merck

Vical
Inovio
VRC

An adenoviral-vector-based approach for pandemic influenza vaccine

Advantages for using Non-replicatingadenoviral vectors expressing avian HA (HAd-H5HA)

- Egg-independent strategy
- Vaccine qualified cell lines are available
- Safety profile is known
- No need for high containment
- Millions of doses of vaccine can be made within a reasonable time i.e., 30 days
- Effectively delivered by mucosal/parental route
- Non-pathogenic for their natural hosts
- No integration into the host genome

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Development of adenoviral-vector-based pandemic influenza vaccine against antigenically distinct human H5N1 strains in mice

Mary A Hoelscher, Sanjay Garg, Dinesh S Bangari, Jessica A Belser, Xiuhua Lu, Iain Stephenson, Rick A Bright, Jacqueline M Katz, Suresh K Mittal, Suryaprakash Sambhara

Lancet (2006)

New Pre-pandemic Influenza Vaccines: An Egg- and Adjuvant-independent Human Adenoviral Vector Strategy Induces Long-lasting Protective Immune Responses in Mice

MA Hoelscher[1,3], L Jayashankar[2,3], S Garg[1], V Veguilla[1], X Lu[1], N Singh[2], JM Katz[1], SK Mittal[2] and S Sambhara[1]

Clin Pharmacol Ther (2007)

A Broadly-Protective Pandemic Influenza Vaccine Against Clade 1 and Clade 2 H5N1 viruses

Mary A. Hoelscher†, Neetu Singh1†, Sanjay Garg, Lakshmi Jayashankar1, Vic Veguilla, Aseem Pandey1, Yumi Matsuoka, Jacqueline M. Katz, Ruben Donis, Suresh K. Mittal1*, and Suryaprakash Sambhara*

J Infect Dis (2008)

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Conclusions

HAd-H5HA is

- **Immunogenic**
- **induces long-lasting humoral and cellular responses**
- **Confers protection against homologous as well as antigenically distinct strains of H5N1 viruses**
- **Inclusion of conserved proteins broadens the immune response**

Phase 1 clinical trial with Ad4-H5HA was completed by PaxVax. Oral delivery as a tablet and the cost per dose is $0.10

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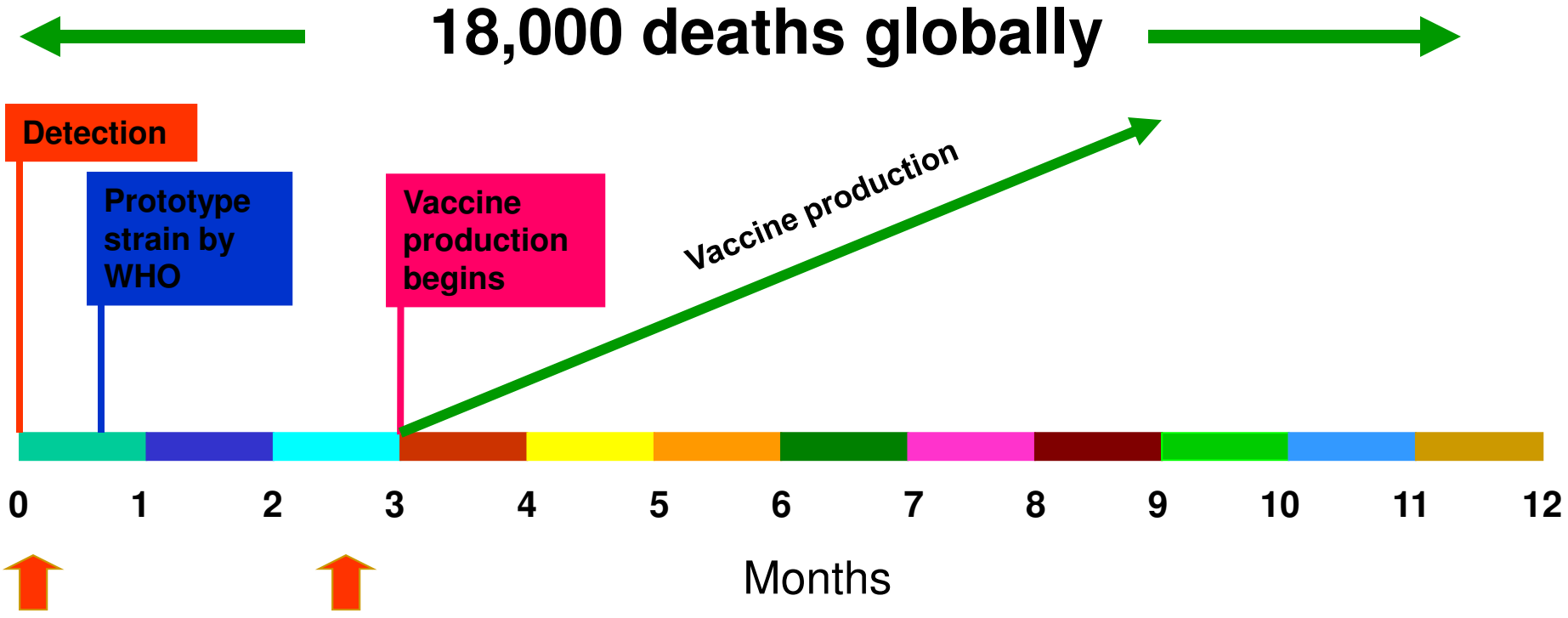
If Pandemic strain is distinct from the stockpiled Pre-pandemic vaccines and not even an H5N1,

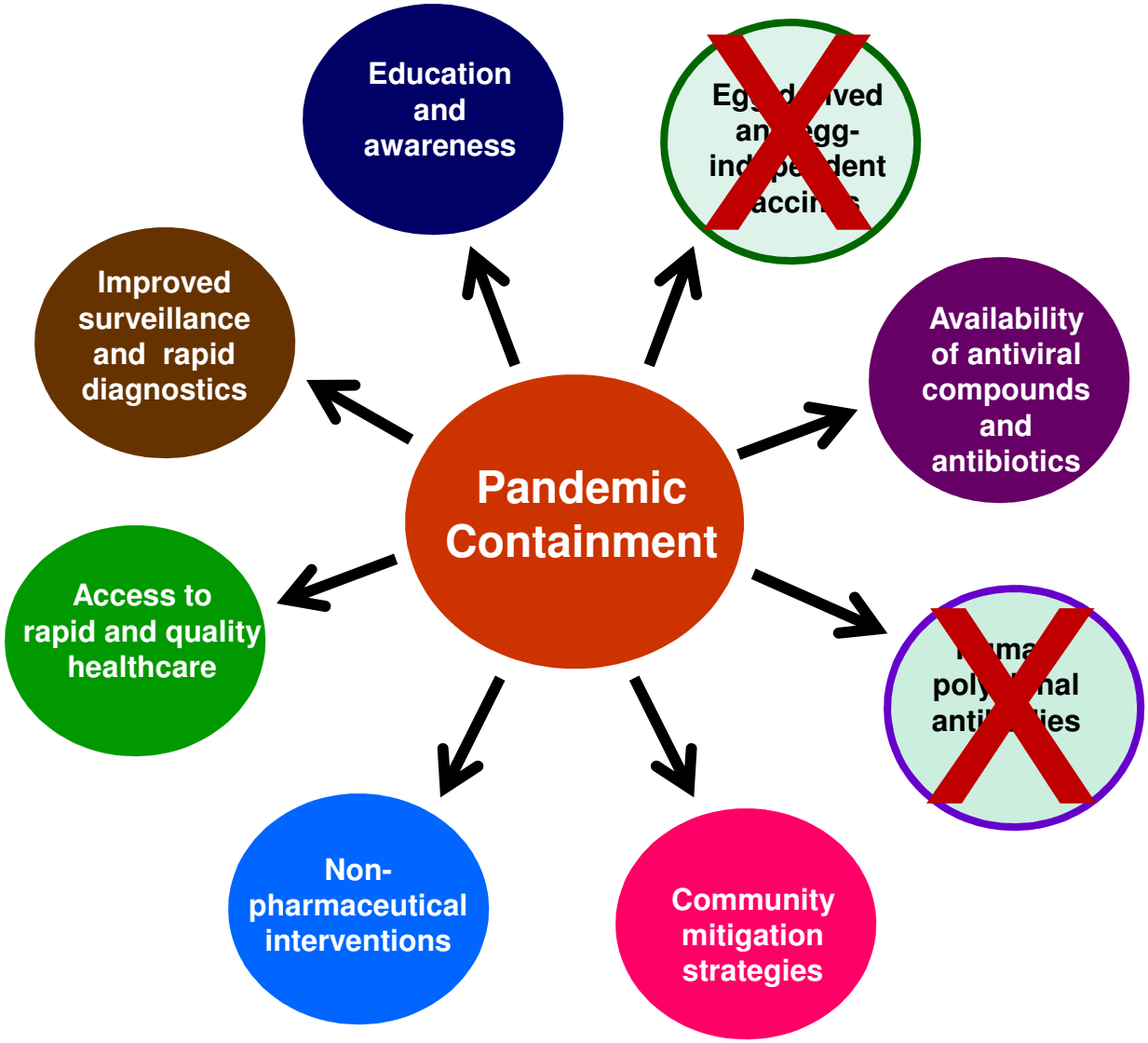
What technologies are available to make a Pandemic vaccine in the shortest possible time-frame to contain the pandemic?

2009 Novel A/H1N1 pandemic

Developing Vaccine against pandemic influenza virus in a pandemic



Global Public Health Measures to contain a pandemic



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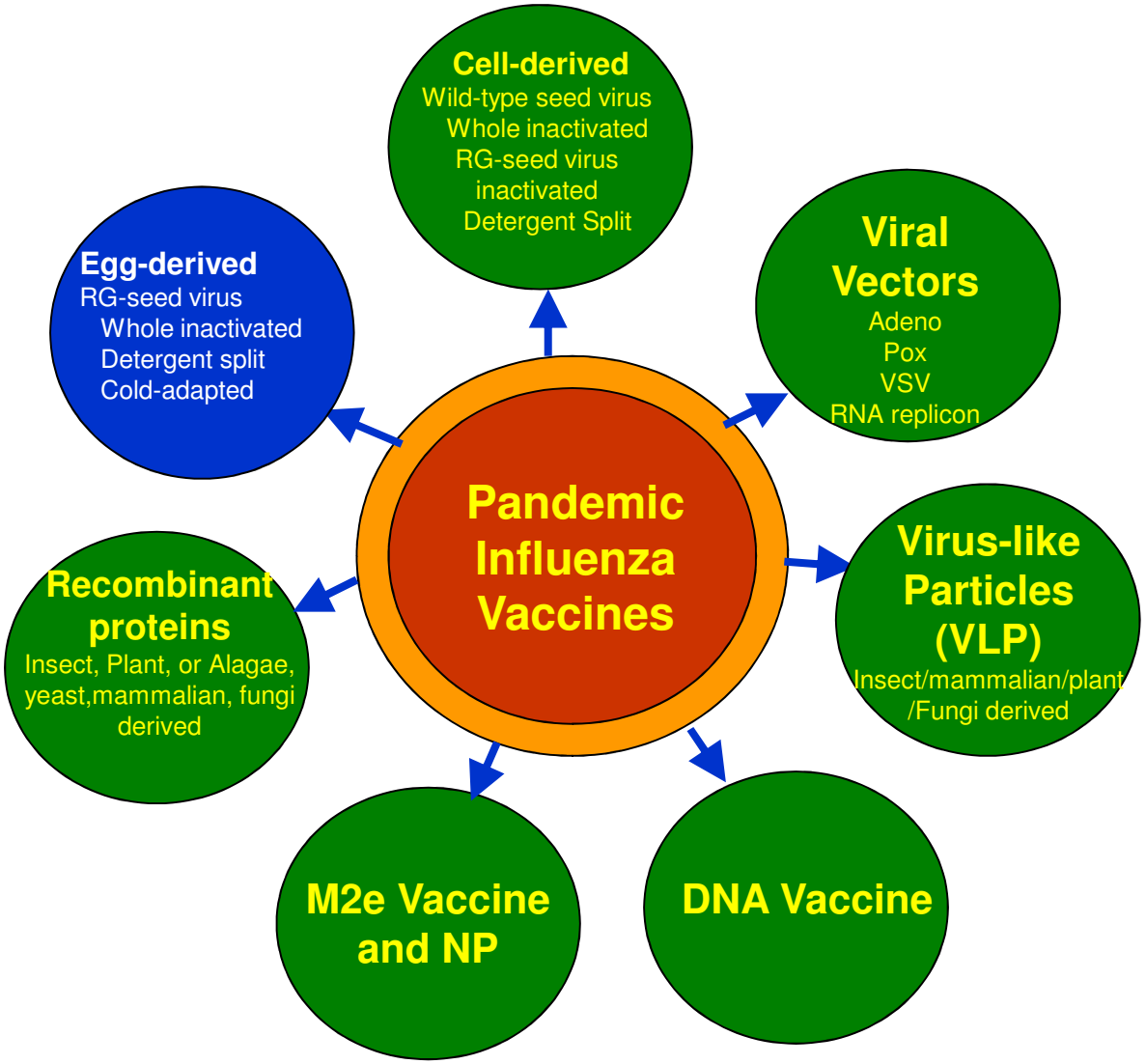
Vaccine Production Technologies
Concept to Customer: Limitations & Hurdles



- **Which technology? Technology transfer issues**
- **Antigen production timeline**
- **Access to Adjuvants**
- **Regulatory requirements**

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